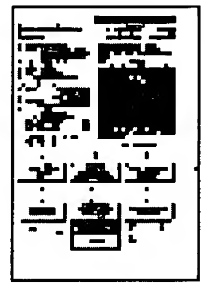
The Delphion Integrated View

Title: JP2000290289A2: PRODUCTION OF 1-HALOGENO-2-DEOXYRIBOFURANOSE DERIVATIVE

Derwent Title: Preparation of 1-halogeno-2-deoxyribofuranose derivatives comprising halogenation of 20deoxyribofuranose derivatives [Derwent Record]



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Abstract:

PROBLEM TO BE SOLVED: To obtain a 1-halogeno-2-deoxyribofuranose derivative useful as a raw material for 2'-deoxynucleoside derivatives by reacting a specific 2-deoxyribofuranose with a hydrogen halide gas and further with an acyl halide.

SOLUTION: This method for producing a 1-halogeno-2-deoxyribofuranose derivative of formula II (X is a halogen) [for example, 1-chloro-3,5-bis(4- chlorobenzoyl)-2-deoxyribofuranose] comprises blowing dry hydrochloric acid gas through the aprotic solution of a compound of formula I [R1 is a (substituted) 1-4C alkyl; R2, R3 are each a 1-4C alkyl or (substituted)benzyl] [for example, 3,5-bis(4-chlorobenzoyl)-2-deoxy-1-methylribofuranose] for 0.5 to 3 hr, further subjecting the mixture to the reaction for 0.5 to 2 hr, dropwisely adding acetyl chloride to the reaction solution for 0.5 to 3

2000-290289

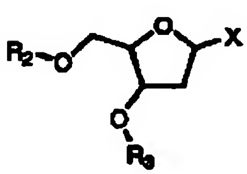
[Title of the Invention]

PRODUCTION METHOD OF 1-HALOGENO-2-DEOXYRIBOFURANOSE DERIVATIVE

[Abstract]

The invention provides a production method of a 1-halogeno-2-deoxyribofuranose derivative which solves problems of a low reaction yield, production of byproducts difficult to separate, undesirable environmental effects and the like in conventional methods. That is, the production method is for producing a 1-halogeno-2-deoxyribofuranose derivative defined by the following formula (2):

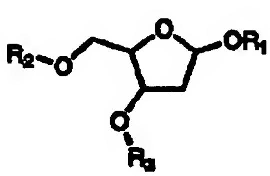
(kagaku 2)



(2)

by causing reaction of a 2-deoxyribofuranose derivative defined by the following formula (1):

(Kagaku 1)



(1)

with a hydrogen halide gas in a non-protonic solvent and successively with an acyl halide or thionyl halide. The invention provides a method for safely producing a 1-halogeno-2-deoxyribofuranose derivative with high purity in

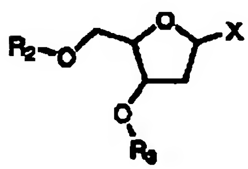
industrial scale.

[Claims]

[Claim 1]

A method for producing a 1-halogeno-2-deoxyribofuranose derivative defined by the following formula (2):

(kagaku 2)

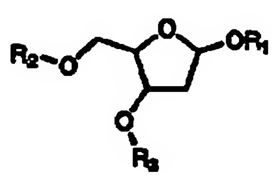


(2)

wherein R_2 and R_3 independently denote an alkyl having 1 to 4 carbon atoms, a benzyl optionally substituted with an alkyl having 1 to 4 carbon atoms or a halogen atom, an aliphatic acyl having 2 to 4 carbon atoms, or an aromatic acyl optionally substituted with an alkyl having 1 to 4 carbon atoms or a halogen atom; and X denotes a halogen atom:

by causing reaction of a 2-deoxyribofuranose derivative defined by the following formula (1):

(kagaku 1)



(1)

wherein R_1 denotes an alkyl having 1 to 4 carbon atoms and optionally substituted with a halogen atom; R_2 and R_3 independently denote same as those in the formula (2):

with a hydrogen halide gas in a non-protonic solvent and successively with an acyl halide or thionyl halide.

[Claim 2]

The method for producing a 1-halogeno-2-deoxyribofuranose derivative according to claim 1, wherein R_1 denotes an alkyl having 1 to 3 carbon atoms and optionally substituted with a halogen atom and R_2 and R_3 independently denote an aromatic acyl optionally substituted with an alkyl having 1 to 4 carbon atoms or a halogen atom.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

The invention relates to a production method of 1-halogeno-2-deoxyribofuranose derivative useful as a raw material of a 2'-deoxynucleoside derivative.

[0002]

[Prior Art]

As methods for producing a 1-halogeno-2-deoxyribofuranose derivative have been knows the following methods:

(1) a method of causing reaction of a 3,5-diacyl-2-deoxy-1 methylribofuranose derivative with acetyl halide in the presence of an alcohol (reference to Japanese Patent Application Laid-Open (JP-A) No. 7-224081):

(2) a method of causing reaction of 3,5-bis(4-chlorobenzoyl)-2-deoxy-1-methylribofuranose with hydrogen chloride gas (reference to Journal of Organic Chemistry,

34, 3806 (1969): and

(3) a method of causing reaction of a 3,5-diacyl-2-deoxy-1-methylribofuranose derivative with acetyl halogen in an acetic acid solvent (reference to JP-A No. 62-12790).

[0003]

Among the above-mentioned methods for producing a 1-halogeno-2-deoxyribofuranose derivative, (1) the method of causing reaction with acetyl halide in the presence of an alcohol produces a byproduct due to the dissociation of the protection groups of the ribose. It is difficult to remove the byproduct from the aimed product and it results in low separation yield of the aimed product and need of an increased number of steps and therefore the method is not suitable for an efficient industrial method. Also, (2) the method of using hydrogen chloride gas is difficult to involve the raw material entirely in the reaction. Therefore, the reaction yield is low and the raw material is difficult to be separated from the aimed product and thus refining of the aimed product further lowers the separation yield of the product and requires an increased number of steps and accordingly the method is not an efficient industrial method. Further, (3) the method of causing reaction with acetyl halide in an acetic acid solvent needs to use a large quantity of an acid halide compound and therefore has a diffusion problem of mist of the acid halide compound undesirable in working

environments.

[0004]

[Problems to be Solved by the Invention]

The aim of the invention is to provide a production method of a 1-halogeno-2-deoxyribofuranose derivative which solves conventional problems that a byproduct difficult to separate is produced: that reaction is incomplete and a raw material difficult to separate remains: and that a large quantity of an acid halide compound undesirable in a working environments is employed.

[0005]

[Means for Solving the Problem]

In order to solve the above-mentioned problems, the inventors of the invention have made various investigations on a method of producing a 1-halogeno-2-deoxyribofuranose derivative with high purity, at high yield, and easily by industrial production.

[0006]

Consequently, the inventors have found that in the case reaction of a 2-deoxyribofuranose derivative with a hydrogen halide gas and successively with an acyl halide or thionyl halide is caused in a non-protonic solvent, surprisingly the reaction proceeds quantitatively and thus a high purity 1-halogeno-2-deoxyribofuranose derivative is safely and efficiently produced without leaving the raw material or without

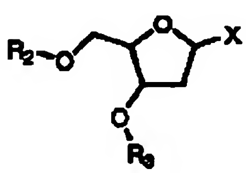
being accompanied with production of a byproduct derived from the raw material and accordingly at a remarkably high isolation yield as compared with conventional methods. The findings have now led to completion of the invention.

[0007]

That is, the invention provides a method for producing a 1-halogeno-2-deoxyribofuranose derivative defined by the following formula (2):

[0008]

(kagaku 4)



(2)

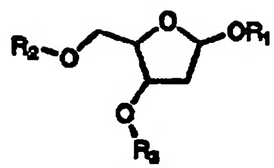
[0009]

wherein R_2 and R_3 independently denote an alkyl having 1 to 4 carbon atoms, a benzyl optionally substituted with an alkyl having 1 to 4 carbon atoms or a halogen atom, an aliphatic acyl having 2 to 4 carbon atoms, or an aromatic acyl optionally substituted with an alkyl having 1 to 4 carbon atoms or a halogen atom; and X denotes a halogen atom:

by causing reaction of a 2-deoxyribofuranose derivative defined by the following formula (1):

[0010]

(kagaku 3)



(1)

[0011]

wherein R_1 denotes an alkyl having 1 to 4 carbon atoms and optionally substituted with a halogen; R_2 and R_3 independently denote same as those in the formula (2):

with a hydrogen halide gas in a non-protonic solvent and successively with an acyl halide or thionyl halide.

[0012]

[Best Modes of the Embodiments of the Invention]

Hereinafter, the invention will be described more in detail. In the formula (1), examples of the alkyl having 1 to 4 carbon atoms as denoted by R^1 are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl and preferable examples are methyl, ethyl, and isopropyl. Examples of the halogen atom-substituted alkyl having 1 to 4 carbon atoms are chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1-chloroethyl, 1,2-dichloroethyl, 1-bromoethyl, 1,2-dibromoethyl, chloroisopropyl, chlorobutyl, chloroisobutyl, bromoisopropyl, bromobutyl, and bromoisobutyl. Examples of the alkyl having 1 to 4 carbon atoms as denoted by R_2 and R_3 are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl and preferable examples are methyl, ethyl, and isopropyl.

[0013]

Examples of the benzyl substituted with an alkyl having 1 to 4 carbon atoms are 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-ethylbenzyl, 3-ethylbenzyl, 4-ethylbenzyl, propylbenzyl, isopropylbenzyl, isobutylbenzyl, and tert-butylbenzyl. Examples of the benzyl substituted with a halogen atom are 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2,3-dichlorobenzyl, 2,4-dichlorobenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 2,3-dibromobenzyl, and 2,4-dibromobenzyl.

[0014]

Examples of the aliphatic acyl having 2 to 4 carbon atoms are acetyl and propionyl. Examples of the aromatic acyl are benzoyl, toluoyl, 4-chlorobenzoyl, 3-chlorobenzoyl, 2-chlorobenzyol, methoxybenzoyl, and bromobenzoyl. Examples of the aromatic acyl substituted with an alkyl having 1 to 4 carbon atoms are 2-methylbenzoyl, 3-methylbenzoyl, 2-ethylbenzoyl, 2-ethylbenzoyl, 4-ethylbenzoyl, propylbenzoyl, isopropylbenzoyl, butylbenzoyl, and tert-butylbenzoyl. Examples of the aromatic acyl substituted with a halogen atom are 2-chlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2,3-dichlorobenzoyl, 2,4-dichlorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2,3-dibromobenzoyl, and 2,4-dibromobenzoyl.

[0015]

The hydrogen halide gas to be used in the invention may include hydrogen chloride gas, hydrogen bromide gas, and hydrogen iodide gas and as the water content is lower, it is more preferable. The use amount of the hydrogen halide is preferable to be 1 to 10 mole to 1 mole of the starting substance, that is, the 2-deoxyribofuranose derivative.

[0016]

The acyl halide or thionyl halide to be used are those containing the same halogen type as the halogen of the above-mentioned hydrogen halide gas to be used. If this condition is satisfied, aliphatic acyl halides, aromatic acyl halides, and thionyl halides are all usable, however aliphatic acyl halides are preferable owing to easiness of removal after the reaction. More practically, in the case hydrogen chloride gas is used as the hydrogen halide, acetyl chloride, propionyl chloride, and thionyl chloride are preferable. Also, in the case hydrogen bromide gas is used as the hydrogen halide, acetyl bromide, propionyl bromide, and thionyl bromide are preferable. In the case hydrogen iodide gas is used as the hydrogen halide, acetyl iodide, propionyl iodide, and thionyl iodide are preferable. The use amount of the acyl halide or thionyl halide is preferably 0.5 mole to 1 mole and more preferably 0.8 mole to 0.99 mole to 1 mole of the starting substance, that is, the 2-deoxyribofuranose derivative.

[0017]

Any solvent may be used as the non-protonic solvent in the reaction if it is inactive to this reaction. Practical examples may include hydrocarbons such as hexane, cyclohexane, and toluene; halogenated hydrocarbon such as dichloromethane, chloroform, 1,2-dichloroethane, isopropyl bromide, n-butyl chloride, and chlorobenzene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, and 1,4-dioxane; ketones such as acetone, methyl ethyl ketone, and methyl isobutyl ketone; and esters such as ethyl acetate and butyl acetate. These solvents may be used alone and also may be mixed at a proper ratio to be used. The use amount of the non-protonic solvent is preferably adjusted to be 10% by weight to 20% by weight before the reaction of the starting substance, the 2-deoxyribofuranose derivative.

[0018]

The reaction involves consecutive steps of loading the hydrogen halide gas and causing reaction with the acyl halide or thionyl halide. In the step of loading the halogen halide, the reaction temperature is preferably 0°C to 30°C. The time taken for loading is preferably 0.5 hours to 10 hours and more preferably 0.5 hours to 3 hours. Aging reaction after the loading of the hydrogen halide gas is preferably at a reaction temperature of 0°C to 30°C and the reaction time is preferably 0.1 hours to 18 hours and more preferably 0.5 hours to 2 hours.

[0019]

In successive reaction with the acyl halide or thionyl halide in the second step, the reaction temperature is preferably 0°C to 30°C. The time taken for loading is preferably 0.1 hours to 5 hours and more preferably 0.5 hours to 3 hours. Aging reaction after the loading of the acyl halide or thionyl halide is preferably at a reaction temperature of 0°C to 30°C and the reaction time is preferably 0.5 hours to 5 hours and more preferably 0.5 hours to 2 hours.

[0020]

An aimed product, a 1-halogeno-2-deoxyribofuranose derivative is produced by the above-mentioned reaction and precipitated in form of a crystal. The crystal is separated by filtration and dried for recovery. Also, it can be recovered by removing the solvent in reduced pressure, however a recovery method is not limited to these methods. The 1-halogeno-2-deoxyribofuranose derivative obtained in the above-mentioned process may be used as it is for the next reaction or may be refined by recrystallization.

[0021]

[Examples]

Hereinafter, the invention will be described with reference to Example and Comparative Examples.

[0022]

Example 1

A 300 mL-reaction vessel made of glass and whose inside

gas was replaced with nitrogen was loaded with 100 g (48.6 mmol) of diisopropyl ether solution of 20% by weight of 3,5-bis(4-chlorobenzoyl)-2-deoxy-1-methylribofuranose and in the stirring and ice-cooling condition, 18 g of dry hydrogen chloride gas was blown at 3°C to 13°C in 1 hour and the content was stirred further for 0.5 hours at a room temperature (20°C). While the obtained solution was stirred at a room temperature (20°C), 3.3 mL (46 mmol, 0.95 equivalent) of acetyl chloride was dropwise added in 5 minutes and the reaction solution was further stirred for 1 hour at a room temperature. In this stage, the raw materials were all consumed and the reaction was carried out quantitatively. The precipitated crystal was filtered and washed with a small amount of diisopropyl ether. The product was dried at 40°C for 4 hours under reduced pressure to obtain 17.7 g of 1-chloro-3,5-bis(4-chlorobenzoyl)-2-deoxyribofuranose (recovery yield 85%). The product was analyzed by high performance liquid chromatography (reversed-phase column, eluting solution: water/acetonitrile, detection wavelength: 254 nm) to find that 96% by surface area was of the product and no unreacted raw material was observed. The content of 4-chlorobenzoic acid was found 0% by weight by the high performance liquid chromatography and no byproduct derived from protection groups was contained.

Melting point: 122°C

1H-NMR (90MHz, CDCl3, σ(ppm)) 2.7-2.9 (2H, m), 4.5-4.7 (2H, m), 4.7-4.9 (1H, m), 5.5-5.6 (1H, m), 6.5 (1H, d), 7.4-7.5 (4H, m), 7.9-8.0 (4H, m).

[0023]

Comparative Example 1

The conventional method (1) was carried out for reproduction. The result is described as follows.

A 300 mL-reaction vessel made of glass and whose inside gas was replaced with nitrogen was loaded with 10 g (25 mmol) of 3,5-bis(4-chlorobenzoyl)-2-deoxy-1-methylribofuranose and 10 mL of dried cyclohexane and while the contents were stirred under slight pressure of nitrogen, 6.4 g (81 mmol) of acetyl chloride was dropwise added at a room temperature in 5 minutes and successively 0.96 mL of absolute methanol was added. The obtained solution was stirred at 20°C for 4 hours to carry out reaction. Low boiling point substances were removed by distillation from the obtained reaction mixture under reduced pressure and 11 mL of dry cyclohexane was added to the resulting reaction mixture at a room temperature to dissolve the mixture and then stirred for 2 hours under ice-cooling condition. The precipitated crystal was filtered and washed with a small amount of diisopropyl ether. The product was dried at 40°C for 4 hours under reduced pressure to obtain 8.5 g of 1-chloro-3,5-bis(4-chlorobenzoyl)-2-deoxyribofuranose. The product was analyzed by high performance liquid chromatography

(same conditions as those of Example) to find that 90% by surface area was of the product and no unreacted raw material was observed. The quantity of byproducts was measured by the high performance liquid chromatography to find that the content of 4-chlorobenzoic acid was 12% by weight and the yield of the aimed product was 73%. As described, the conventional method (1) was accompanied with production of the byproduct, 4-chlorobenzoic acid derived from the protection groups of the raw material.

[0024]

Comparative Example 2

The conventional method (2) was carried out for reproduction. The result is described as follows.

A 300 mL-reaction vessel made of glass and whose inside gas was replaced with nitrogen was loaded with 100 g (48.6 mmol) of diisopropyl ether solution containing 20% by weight of 3,5-bis(4-chlorobenzoyl)-2-deoxy-1-methylribofuranose and while the solution was stirred under ice-cooling condition, 36 g of dry hydrogen chloride gas was blown at 3°C to 13°C in 3 hours and the resulting solution was stirred further for 3 hours at a room temperature (20°C). The precipitated crystal was filtered and washed with a small amount of diisopropyl ether. The product was dried at 40°C for 4 hours under reduced pressure to obtain 16.2 g of 1-chloro-3,5-bis(4-chlorobenzoyl)-2-deoxyribofuranose. The product was analyzed by high performance liquid chromatography

(same conditions as those of Example) to find that 86% by surface area was of the product and 12% by surface area was of unreacted raw material was observed. The quantity of byproducts was measured by the high performance liquid chromatography to find that the content of 4-chlorobenzoic acid was 0% by weight. According to these results, it was found that the yield of the aimed product was 74% and the raw material remained in the product. As described, in the conventional method (2), the raw material was left and therefore the reaction yield was low and it was difficult to separate the raw material from the product.

[0025]

[Effect of the Invention]

As described, in conventionally known 1-halogeno-2-deoxyribofuranose derivative production methods, there have been problems that an acyl compound derived from a raw material and difficult to be separated is produced as a byproduct: the reaction is not completed to result in low yield: and that the remaining raw material is difficult to be separated from the aimed product. However, according to the invention, if reaction of a 2-deoxyribofuranose derivative with a hydrogen halide gas and successively with an acyl halide or thionyl halide is carried in a non-protonic solvent, surprisingly the reaction proceeds quantitatively and thus a high purity 1-halogeno-2-deoxyribofuranose derivative is safely and industrially produced without being accompanied with production

of a byproduct which is difficult to be separated. Further, in this method, neither a costly catalyst nor a raw material hazardous for handling is required for the production.